Synopsis

Identifier: GM2005/00508/00 **Study Number:** EL110006

Title: A 12-week, randomised, double-blind, placebo-controlled, parallel-group multicentre study to evaluate the anti-inflammatory activity of GW842470 4mg twice daily on pulmonary hyperinflation in subjects with chronic obstructive pulmonary disease (COPD).

Investigator(s): This was a multicentre study.

Study center(s): The study was conducted in 9 countries at 29 sites: Australia (5), Austria (1), Finland (2), Germany (5), Korea (2), New Zealand (1), Russian Federation (3), Slovenia (5), Spain (5).

Publication(s): None at the time of this report

Study Period: 25 Jan 2005 – 15 Sep 2005

Phase of Development: IIa

Objectives: The primary objective of this study was to evaluate the effects of 12 weeks' administration of GW842470 4mg bid or placebo on pulmonary hyperinflation in terms of residual volume measured pre-bronchodilator by plethysmography in subjects with COPD.

The secondary objectives were: to assess efficacy by additional measures of plethysmography and spirometry; to evaluate anti-inflammatory activity by measurement of inflammatory biomarkers; to assess the safety and tolerability of GW842470.

Methodology: This was a Phase IIa, randomized, double-blind, placebo-controlled, parallel-group study. Following a two week run-in period, subjects were randomized to receive one of the following two treatments in a 1:1 ratio:

- GW842470 4mg (4 X 1mg blisters) BID via the DISKUS™ for 12 weeks
- Placebo (4 blisters) BID via the DISKUS for 12 weeks

During the treatment period subjects attended four study visits (after 2, 4, 8 and 12 weeks of treatment). A follow-up visit was attended two weeks after the end of study medication.

Number of subjects:

Number of Subjects	GW842470	Placebo
Planned, N	100	100
Randomised, N	100	107
Completed, n (%)	88 (88)	94 (88)
Total Number of Subjects Withdrawn, n (%)	12 (12)	13 (12)
Withdrawn due to Adverse Events, n (%)	1 (1)	2 (2)
Withdrawn due to Exacerbation of COPD	5 (5)	4 (4)
Withdrawn due to Lack of Efficacy, n (%)	2 (2)	0
Withdrawn for Other Reasons, n (%)	4 (4)	7 (7)

Diagnosis and main criteria for inclusion: Male or female subjects between 40 and 80 years of age with moderate to severe stable COPD, a cigarette smoking history of ≥ 10 pack years, a post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio (FEV_1:FVC) < 0.7; a post-bronchodilator $FEV_1 \geq 30\%$ and $< 80\%$ of predicted normal; evidence of hyperinflation defined as a (pre-bronchodilator) thoracic gas volume at functional residual capacity (TGV_{FRC}) and residual volume (RV) of $\geq 120\%$ of predicted; and a transcutaneous oxygen saturation (SaO_2) of $\geq 88\%$.

Treatment administration: Subjects were instructed to take their study medication for 12 weeks. Each morning and evening subjects took 4 inhalations of GW842470 (1mg/inhalation) (Batch numbers: 041033885 and 051068522) or placebo via DISKUS (Batch numbers: 041033504 and 051066169). In addition subjects could continue to use their salbutamol inhalers (DISKUS or MDI) on a PRN basis and their stable dose of ipratropium bromide (if applicable) for relief medication.

Criteria for evaluation: The primary efficacy evaluation was the change from baseline in pre-bronchodilator RV measured by plethysmography at Week 12.

Secondary efficacy evaluations included total lung capacity (TLC); TGV_{FRC}; airways resistance (Raw); specific airway conductance (sGaw); inspiratory capacity (IC); FVC; FEV_1; FEV_6; forced expiratory flow at 25%-75% of vital capacity (FEF_{25-75}); FEF_{75}; peak expiratory flow rate (PEF); concentration of inflammatory biomarkers in serum samples; Medical Research Council (MRC) Dyspnoea Scale; Symptom Score Scale; Sparse PK samples over 0-6 hours at steady state (Week 8).

Safety evaluations included incidence of adverse events, withdrawals due to exacerbation of COPD, vital signs and clinical laboratory assessments.

Statistical methods: Based on a 2-sided significance level of 5%, and 90% power, 83 subjects were required, per treatment arm, to detect an 8.5% reduction in residual volume at Week 12 on GW842470 compared with placebo. To allow for withdrawals, it was planned to randomize 100 subjects per treatment.

The primary population for efficacy was the Modified intent-to-treat (mITT) population, which included all subjects who were randomised to treatment and had a baseline and at least one on-treatment efficacy or biomarker evaluation. The primary comparison of

interest was the effect of GW84270 versus placebo on the change from baseline in pre-bronchodilator RV measured by plethysmography at Week 12. The comparison was made using log transformed data and a mixed effect model where treatment and treatment by week were fitted as fixed effects, centre was fitted as a random effect, and baseline and baseline by week were fitted as fixed continuous covariates.

Secondary variables assessed by plethysmography and spirometry, and inflammatory biomarkers were also analysed using this mixed effect model. Dyspnoea (MRC scale) and the symptom score scale were analysed using a logistic (proportional odds) model, adjusting for covariates of treatment and baseline values. All safety parameters were listed and summarized.

Summary: The two treatment groups were well matched for all demographic and baseline parameters.

Efficacy

For the primary efficacy variable there was no statistically significant difference between GW842470 and placebo in the change in RV at Week 12.

Summary of the Analysis of Change in Pre-bronchodilator Residual Volume at Week 12 (modified ITT Population)

Week	GW842470 N=96	Placebo N=103
Week 12Adjusted geometric mean	3.987	3.914
Adjusted ratio to baseline	0.979	0.961
GW842470/placebo:		
ratio	1.02	
95% CI	0.98, 1.06	
p-value	0.367	

In the GW842470 group, small decreases in geometric mean RV were observed from baseline to the end of treatment. In the placebo group, there was a slight increase in geometric mean RV at Week 4 compared with baseline and then small decreases at Weeks 8 and 12.

The results of the primary analysis were supported by the secondary efficacy parameters measured by plethysmography and spirometry. A representation of these parameters is presented below. In addition, there was no difference in mean symptom scores between the two treatments as assessed by the MRC Dyspnoea Scale and the Symptom Score Scale.

Summary of Analyses of Secondary Efficacy Parameters Measured by Plethysmography and Spirometry at Week 12 (modified ITT Population)

Parameter		GW842470 N=96	Placebo N=103
TGV_{FRC} (L)	Adjusted mean change from B/L	-0.057	-0.103
	GW842470-placebo: Difference; 95% CL	0.05; -0.11, 0.20	
	p-value	0.566	
TLC (L)	Adjusted mean change from B/L	-0.085	-0.091
	GW842470-placebo: Difference; 95% CL	0.01; -0.14, 0.15	
	p-value	0.931	
sGaw (L/s/kPa)	Adjusted geometric ratio to B/L	1.082	1.082
	GW842470/placebo: ratio; 95% CL	1.0; 0.91, 1.10	
	p-value	0.993	
SVC (L)	Adjusted mean change from B/L	-0.041	0.070
	GW842470-placebo: Difference; 95% CL	-0.11; -0.21, -0.01	
	p-value	0.025	
IC (L)	Adjusted mean change from B/L	-0.008	0.0
	GW842470-placebo: Difference; 95% CL	-0.01; -0.11, 0.10	
	p-value	0.878	
FEV_1 (L)	Adjusted mean change from B/L	-0.003	0.040
	GW842470-placebo: Difference; 95% CL	-0.04; -0.11, 0.02	
	p-value	0.177	
FEF_{25-75} (L/s)	Adjusted geometric ratio to B/L	0.973	0.970
	GW842470/placebo: ratio; 95% CL	1.0; 0.93, 1.09	
	p-value	0.928	
PEF (L/s)	Adjusted mean change from B/L	-0.066	0.072
	GW842470-placebo: Difference; 95% CL	-0.14; -0.34, 0.06	
	p-value	0.181	

TGV_{FRC}=thoracic gas volume at functional residual capacity, TLC=total lung capacity, sGaw=specific conductance, SVC=slow vital capacity, IC=inspiratory capacity, FEV_1=forced expiratory volume in one second, FEF_{75}= forced expiratory flow at 75% of vital capacity; PEF=peak expiratory flow rate

Summary of analysis of systemic inflammation biomarkers: 29 inflammation biomarkers thought to be associated with COPD were assessed in serum samples at baseline, weeks 4, 8 and 12 using a multiplex immunoassay. The difference in adjusted ratios to baseline between GW842470 and placebo treatment groups was statistically significant for prolactin at week 12 (p=0.024). The adjusted geometric mean for GW842470 was 1115.9

pg/mL (ratio to baseline 0.917) relative to 1297.0 pg/mL for placebo (ratio to baseline 1.066). No other statistically significant differences were observed between treatment groups.

Safety: A summary of the most 10 frequent adverse events (AEs) on therapy are presented below. Slightly more AEs were reported during treatment with GW842470 than with placebo but overall the incidence of individual AEs was low for both groups.

Most Frequent Adverse Events During Treatment (Safety Population)

Ten Most Frequent Adverse Events During Treatment	GW842470 N=100	Placebo N=107
Subjects with any AE(s), n (%)	34 (34)	27 (25)
Headache	5 (5)	3 (3)
Back Pain	4 (4)	2 (2)
Rhinitis	3 (3)	3 (3)
COPD	3 (3)	0
Chest Pain	3 (3)	0
Nasopharyngitis	2 (2)	2 (2)
Dyspnoea	2 (2)	0
Epistaxis	2 (2)	0
Arthralgia	2 (2)	1 (<1)
Pain in Extremity	2 (2)	0
Eczema	2 (2)	1 (<1)
Hypertension	2 (2)	0
Upper Respiratory Tract Infection	1 (1)	3 (3)
Herpes Simplex	0	2 (2)

The number of subjects reporting a drug-related AE was 10 (10%) in the GW842470 group and 6 (6%) in the placebo group. The most frequent drug-related individual AEs were rhinorrhoea, headache and eczema, each reported by 2 (2%) subjects in the GW842470 group. The highest number of drug-related AEs reported by body system was those related to gastrointestinal disorders occurring in 4 (4%) subjects in the GW842470 group, but each individual gastrointestinal AE (upper abdominal pain, constipation, nausea and stomatitis) was reported by 1 (1%) subject only.

During treatment, one subject in the placebo group had a fatal serious AE of myocardial infarction; this was not assessed as drug-related. Non-fatal SAEs were reported by 5 (5%) subjects in the GW842470 group and 1 (1%) in the placebo group. Of these, one subject was withdrawn (GW842470 group) but none of the events were assessed as related to treatment.

There were no clinically significant changes in laboratory haematology or biochemistry parameters, vital signs or 12 lead ECG results following either treatment.

Conclusions:

- Treatment with GW842470 4mg bid for 12 weeks did not significantly reduce pre-bronchodilator residual volume and had no consistent effect on other indices of lung function compared with placebo
- Treatment with GW842470 4mg bid for 12 weeks did not have a clinically significant effect on systemic inflammation biomarkers compared with placebo
- GW842470 4mg bid was generally well tolerated resulting in a low incidence of gastrointestinal events with no evidence of any significant safety risk compared with placebo
- The efficacy results of this study do not support the use of GW842470 4mg bid in subjects with moderate to severe COPD

Date of Report: July 2006